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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
05/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66,70-75 and 78-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66, 70-75 and 78-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/26/07 has been entered.

Applicant's response filed 3/26/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/25/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

Claims 66, 70-75 and 78-82 are pending in the application.

Applicant's arguments and/or amendments filed on 3/26/07, with respect to the rejections under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, these rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the instant amendments.

Response to Amendment

The reply filed on 3/26/07 is not fully responsive to the prior Office Action because of the following omission(s) or matter(s): the status of the claims is incorrect. Claims 79-82 are labeled "new", although they were previously presented. See 37 CFR 1.111. In response to this action, applicant is required to supply the omission or correction in order to avoid abandonment.

New Objections/Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66, 70-75 and 78-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The claims are directed to an oligonucleotide wherein "said oligonucleotide comprises a first region consisting of ten contiguous 2'-deoxy nucleosides flanked by second and third wing regions, each of said second and third wing regions independently consisting of five 2'-O-methoxyethyl nucleosides", which constitutes new

matter. The specification does not contemplate these limitations and hence does not provide support for such. These limitations were first introduced in the amendment to the claims filed 3/26/07.

Furthermore, there is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 5/20/99, which is the filing date of the instant application.

Applicant's arguments filed 3/26/07 point to support for the amendments to the claims on page 29 of the instant specification. A review of the specification, and particularly page 29, does not reveal support for where the various claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 3/26/07.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 66, 70-75 and 78-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. (WO 96/40266), in view of Nicklin et al. (WO 98/09633) and Yu et al. (Bioorganic & Medicinal Chemistry, Vol. 4, No. 10, pages 1685-1692, 1996).

The invention of the above claims is drawn to a method of administering an oligonucleotide into the lung of a mammal, comprising aerosolizing the oligonucleotide and introducing the aerosolized oligonucleotide into the lung of the mammal, wherein said oligonucleotide comprises a first region consisting of ten contiguous 2'-deoxy nucleosides flanked by second and third wing regions, each independently consisting of five 2'-O-methoxyethyl nucleosides, and the oligonucleotide is taken up by at least one cell type in the lung. The oligonucleotide is in an aqueous media such as sterilized, pyrogen free water or saline solution or in a saline solution or a powder. The invention is further drawn to a method of increasing uptake into lung cells of a phosphorothioate containing oligonucleotide delivered by pulmonary administration into lung cells comprising incorporation of a 2'-O-methoxyethyl modification into the oligonucleotide.

Nyce et al. teach that respirable antisense oligonucleotides can be formulated to be liquid or solid (see page 10). Liquid compositions comprise the antisense compound and sterile, pyrogen free water or saline solution (see page 9, for example). Nyce et al. teach that suitable formulations for delivery include powders (see page 12). Nyce et al. teach that respirable antisense oligonucleotides can be formulated into powders and effectively delivered with a metered dose inhaler. Nyce et al. teach methylphosphonate and phosphorothioate linkages to render respirable antisense oligonucleotides more stable *in vivo* (see page 7).

Nyce et al. teach that particles comprised of antisense compound should be of respirable size that is particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Nyce et al. teach

that in general, particles ranging from about .5 to 10 microns in size are respirable (see page 10). Therefore, Nyce et al. teach respirable particles "about 1 to about 5 microns", as instantly recited.

Nyce et al. teach a method of administering the aerosolized antisense oligonucleotides to animals *in vivo* (see page 16, for example) and teach uptake of the oligonucleotide in the lungs.

Nyce et al. do not teach 2'-O-methoxyethyl 2'-deoxy wings as instantly claimed.

Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminooxyalkyl modifications. Nicklin et al. teach phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5).

Yu et al. teach hybrid oligonucleotides comprising phosphorothioates and 2'-O-methyl nucleoside that have greater activity and are more resistant to nuclease-mediated degradation than oligonucleotides with phosphorothioates only. The hybrid oligonucleotides are deoxyribonucleoside phosphorothioates flanked by two segments of contiguous 2'-O-methyl ribonucleoside phosphorothioates at the ends (see page 1685 and figure 1). For example, Yu et al. teach a gapmer oligonucleotide that comprises a first region of fifteen phosphorothioates flanked by two regions of five 2'-O-methyl ribonucleoside phosphorothioates (see oligonucleotide #3 in Figure 1).

It is noted that the instant claims recite "wherein said oligonucleotide comprises a first region consisting of ten contiguous 2'-deoxy nucleosides flanked by second and third wing regions, each independently consisting of five 2'-O-methoxyethyl nucleosides." The term "consisting" does not limit the term "comprising" and therefore the oligonucleotides can comprise bases outside of the instantly recited sizes.

It would have been obvious to incorporate 2'-O-methoxyethyl modifications, as taught by Nicklin et al. into the antisense oligonucleotides taught by Nyce et al. and it would have been obvious to incorporate a region of 2'-deoxy nucleosides flanked by two 2'-O-methoxyethyl wings into the antisense oligonucleotides taught by Nyce et al.

One would have been motivated to incorporate 2'-O-methoxyethyl modifications because Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target. Since Nyce et al. teach other modifications, such as incorporation of phosphorothioates, in order to render the respirable antisense oligonucleotides more stable *in vivo*, one would have been motivated to incorporate 2'-O-methoxyethyl modifications as well since they were also known in the art to enhance oligonucleotide activity, as evidenced by Nicklin et al.

Furthermore, one would have been motivated to incorporate the 2'-O-methoxyethyl modifications into the instantly recited configuration of comprising a first region consisting of ten contiguous 2'-deoxy nucleosides flanked by second and third wing regions, each independently consisting of five 2'-O-methoxyethyl nucleosides because Yu et al. teach this gapmer configuration and teach that hybrid

oligonucleotides comprising phosphorothioates and 2'-O-methyl nucleosides have greater activity and are more resistant to nuclease-mediated degradation than oligonucleotides with phosphorothioates only. Additionally, Yu et al. teaches a specific example wherein the gapmer oligonucleotide comprises a first region of fifteen phosphorothioates flanked by two regions of five 2'-O-methyl ribonucleoside phosphorothioates.

Since each of the instantly recited modifications were known in the art to benefit oligonucleotide stability and delivery and furthermore it was known in the art that gapmers with a 2'-deoxy region and two 2'-O-modified wing regions also yield oligonucleotides with greater activity and more resistance to nuclease-mediated degradation, as evidenced by Yu et al.

Finally, one would have a reasonable expectation of success to that the chemical modifications taught by Nicklin et al. and Yu et al. would benefit the antisense oligonucleotides of Nyce et al. because each of the instantly recited modifications, as well as the specific configuration of modifications, were known in the art at the time the invention was made to enhance the activity of antisense oligonucleotides, as evidenced by Nicklin et al., Nyce et al. and Yu et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H Bowman
Examiner
Art Unit 1635

AHB

JON E. ANGELL, PH.D.
PRIMARY EXAMINER